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NARRATIVE REVIEW

State of the art: Renal recovery after AKI - from basic science to clinical practice

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Abstract

Purpose: Acute kidney injury (AKI) is common in critically ill patients and associated with a high risk of mortality, chronic kidney disease (CKD) and cardiovascular morbidity. The risks are higher in patients with incomplete or no renal recovery. The purpose of this review is to summarize the current understanding of the mechanisms of renal recovery, list some key risk factors for nonrecovery and highlight knowledge gaps.

Methods: Narrative review of key data in the literature.

Results: Recovery from AKI is an active process. When damage to the kidney is mild, full regeneration is possible; with extensive damage, fibrosis sets in. Current strategies to achieve renal recovery focus on identification of the mechanism of injury and minimizing further insults. Nephrotoxic exposures and various forms of dialytrauma impair recovery. The likelihood that repair will be maladaptive increases with age and extent/duration of injury. Return of glomerular filtration rate to pre-injury levels does not exclude nephron loss and development of CKD. Post-discharge follow-up of AKI survivors is important, but there are ongoing uncertainties and clinical practice is variable. Research is ongoing to determine the role of pharmacological interventions.

Conclusions: The prognosis of AKI is critically tied to renal recovery, and there is great urgency to identify effective therapies.

Keywords: Acute kidney injury, AKI, Recovery, Renal repair, Persistent AKI

Introduction

Acute kidney injury (AKI) is a multi-factorial syndrome with different trajectories and variable renal and non-renal outcomes [1]. In most cases, renal repair occurs, ideally leading to recovery, implying that glomerular and tubular function reach baseline status. However, recovery can range from complete to partial, and patients may be left with chronic kidney disease (CKD) of whom a proportion progresses to end-stage kidney disease (ESKD) and dialysis-dependency [2–6] (Fig. 1). Due to the absence of serial kidney biopsies, the relative importance and temporal sequence of different repair mechanisms remain largely undefined. In a retrospective cohort study of 16,968 critically ill patients with stage 2 or 3 AKI, 41% of patients had not fully recovered kidney function at the time of hospital discharge [3]. Of these patients, 26% had no AKI reversal at any point, and 15% had reversal but relapsed without subsequent recovery. Others have reported noticeable impairment of quality of life in AKI survivors and a high risk of death within the first months after AKI [7, 8]. There is an urgent need to identify patients at highest risk of non-recovery and to determine whether the outcomes can be altered by pharmacological or non-pharmacological interventions.

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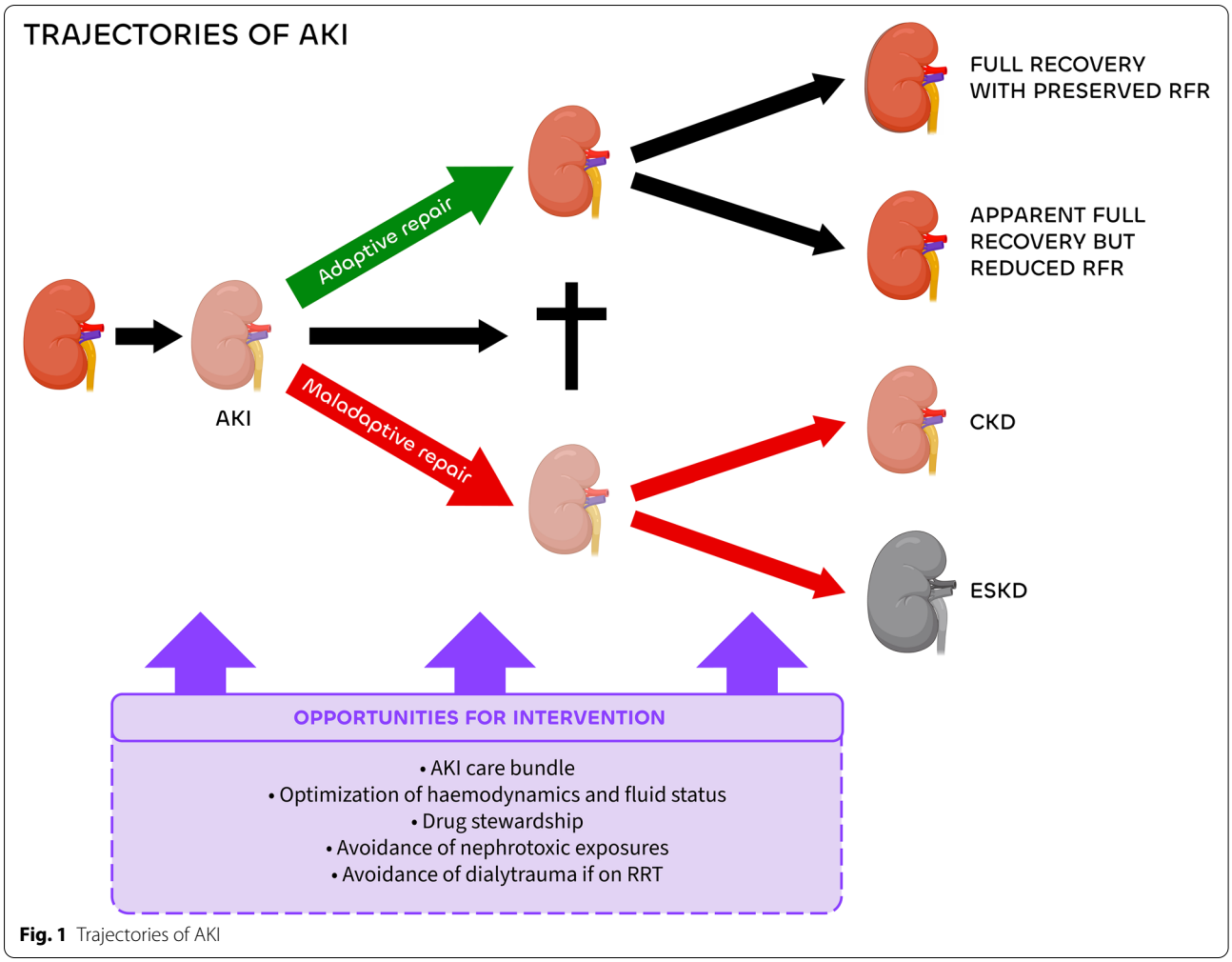

Fig. 1 Trajectories of AKI

Definition of renal recovery

The criteria to define renal recovery vary [3, 9–23] (Table 1). Rapid recovery of renal function is often defined as resolution of AKI within 48–72 h (i.e., transient AKI). It has been associated with better renal and non-renal outcomes compared to persistent AKI lasting for 72 h or more [9]. AKI is part of acute kidney disease (AKD) defined as acute kidney dysfunction lasting up to 90 days [25]. Both, AKI and AKD are associated with risk of progression to CKD.

Accurate assessment of baseline renal function is fundamental for evaluating the degree of recovery after AKI. The baseline renal function is typically defined as the kidney function prior to AKI development and serves as the reference point for assessing AKI severity and degree of recovery. A 90–365-day window before onset of AKI is often used in clinical studies, although recognizing that this information is lacking in many patients and that renal function might not be at steady state leading up to hospital admission. When historical data are unavailable, surrogate methods such as back-calculation of serum creatinine based on an assumed estimated glomerular filtration rate (eGFR) (e.g., 75 mL/min/1.73 m^2 for healthy adults) have been recommended [21]. However, this method may introduce inaccuracies and may miss unknown CKD. There have been a number of changes in formulas and the choice differs across the world but no equation is perfectly accurate [26, 27]. An alternative is to use the serum creatinine value at hospital admission as the reference. However, with that scenario, baseline renal function may be underestimated as some patients may already have AKI when presenting to the hospital and renal recovery may be overestimated (Fig. 2). Another option is to use the lowest serum creatinine value during hospital stay. With this approach, there is a risk of overestimating the incidence of AKI as serum creatinine values may be low due to confounding factors like muscle wasting, liver disease or hemodilution following fluid administration [27].

Table 1 Definitions of renal recovery used in the literature and associated outcomes

Determining factor	Terminology	Definition	Outcome
AKI duration	Transient or rapid reversal AKI	Return to baseline kidney function within 48–72 h	• Persistent severe AKI was associated with an increased risk of 90-day mortality, hospital readmission, and a lower probability of renal recovery [9] • Longer duration of AKI was associated with increasing rates of heart failure, ischemic heart disease, peripheral artery disease, CKD and long-term mortality [10, 11]
	Persistent AKI	Persistence of AKI beyond 72 h from onset	
Degree of recovery [12]	Non-recovery of kidney function	Ongoing need for RRT	• Post-AKI kidney function and baseline kidney function, but not severity, were independently associated with all-cause mortality, MACEs, ESKD, and readmission [13] • AKI during a hospital admission was associated with increased subsequent renal progression even if post-episode kidney function was normal [14]
	Incomplete recovery of kidney function	Resulting in CKD stages 1–3	
	Partial recovery of kidney function	SCr concentration between baseline and 1.5 times baseline or other evidence of ongoing injury such as proteinuria or loss of renal functional reserve	
	Full recovery	SCr < 1.5 times baseline	
Degree of recovery [15]	Recovery	Decrease of SCr from the reference value of at least 33% in the following 7 days	In COVID-19 survivors with AKI who were discharged, 35% had not recovered to baseline kidney function by the time of discharge; an additional 36% of patients who had not recovered kidney function at discharge did so on post-hospital follow-up [16]
Degree of recovery [17]	Complete recovery	Improvement in eGFR to within 90% of baseline value	Reversible AKI was associated with a significant risk of de novo CKD (HR 1.91) and death (HR 1.50) [17]
Degree of recovery [18]	Recovery	SCr post-AKI within 25% of the baseline (pre-hospitalization value) and no RRT dependency	Participants who did not recover kidney function had a higher risk for mortality (HR 1.26) and adverse renal outcomes (HR 4.13) compared with recovered patients [18]
Non dialysis [19]	Liberation from RRT	Liberation of RRT at 60 days from start of RRT [19]	Kidney failure due to AKI confers a higher risk of mortality in the first 6 months compared with kidney failure due to diabetes or other causes
Change in SCr from baseline [20]	Complete recovery	SCr level no more than 0.5 mg/dL (44 µmol/L) above baseline	In a cohort of post cardiac surgery patients, both AKI with complete and incomplete renal recovery were risk factors for 3-year major adverse events
	Incomplete recovery	SCr more than 0.5 mg/dL above baseline value but no RRT dependency	
	No recovery	RRT dependency	
eGFR [21]	Complete recovery	eGFR ≥ 60 ml/min/1.73m^2	In a cohort of post cardiac surgery patients, only incomplete but not complete renal recovery was a risk factor for 3-year major adverse events [22]
	Incomplete recovery	eGFR < 60 ml/min/1.73m^2	
	No recovery	RRT dependency	
Pattern of recovery	Early sustained reversal	Reversal starting within 7 days and sustained through hospital discharge	Early reversal of AKI was associated with the shortest ICU and hospital lengths of stay and best prognosis. Age-adjusted survival was highest in early sustained reversal > late sustained reversal > relapse recovery > relapse no recovery > no-recovery [3]
	Late sustained reversal	Defined as reversal after 7 days and sustained through hospital discharge	
	Relapse recovery	Reversal after AKI stage 2–3 with subsequent AKI and complete recovery at hospital discharge	
	Relapse with no recovery	Reversal after AKI stage 2–3 with subsequent AKI and non-recovery at hospital discharge	
	Non-recovery	Never reversed AKI	

Table 1 (continued)

Determining factor	Terminology	Definition	Outcome
AKD	AKD	Acute kidney dysfunction and/or evidence of structural damage for up to 90 days	Both AKI and AKD were associated with significantly increased mortality versus those without kidney disease and demonstrated a substantial increase in the risk of both CKD and ESKD among both AKI and AKD without AKI cohorts [23]

Abbreviations: AKD acute kidney disease, *AKI* acute kidney injury, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESKD* end-stage kidney disease, *HR* hazard ratio, *ICU* intensive care unit, *MACE* major adverse cardiac events, *RRT* renal replacement therapy, *SCr* serum creatinine

Mechanisms of renal recovery

The transition from AKI to renal recovery or non-recovery and development or worsening of CKD appears to be the result of a balance between adaptive (leading to recovery) and maladaptive (leading to dysfunction and fibrosis) repair processes (Fig. 3). Our understanding of these mechanisms remains limited. However, basic science has provided important insights. Adaptive repair depends on the capacity of immature tubular cells to replace epithelial cells and regenerate nephron segments [28]. Some parietal cells (CD133+, CD24+) represent renal progenitor cells that have the capacity to differentiate into renal epithelial cell types or migrate to the glomerulus and replace senescent podocytes [29, 30]. Monocytes appear to play a dual role in AKI through polarization towards the predominantly pro-inflammatory M1 and anti-inflammatory M2 phenotypes. The release of chemotactic factors like chemokine C–C-motif chemokine ligand 14 (CCL14) by damaged epithelial cells promotes intrusion of T cells and monocytes into the renal interstitial compartment and monocyte transformation to macrophages [31]. M2 macrophages contribute to epithelial regeneration, clearance of intraluminal debris, attenuation of inflammation and repair [28]. Klotho, a pleiotropic protein with multifaceted functions is one of the factors that regulate fibroblast growth factor signaling and stimulate macrophage polarization towards the anti-inflammatory M2 phenotype [32]. Loss of Klotho is an early event in the AKI-to-CKD transition [33].

Damage of cellular DNA and activation of the DNA-damage response leads to cell cycle arrest [28]. This cellular senescence, associated with kidney repair and regeneration, has been observed in proximal tubular cells, glomerular podocytes and endothelial cells and is mediated through a detrimental secretome termed the senescence-associated secretory phenotype (SASP) [34]. SASP activates NF-kB pathway and leads to the release of pro-inflammatory mediators such as IL-6, IFN-γ, IL-1b 1, TNF-a and MCP-1 [35]. Cellular polyploidization, a process during which cells increase their DNA content without dividing and grow in size, plays a role in tissue growth and repair of many organs [36]. However, the exact role of polyploid cells in the kidney and the implications for repair or secondary damage remain uncertain. Studies in humans and animals have demonstrated the feasibility of a multiomics approach to discovering non-invasive markers of maladaptation and adverse clinical outcomes [37].

Maladaptive repair is associated with endothelial to mesenchymal transformation, necrosis of tubular cells and development of tubulointerstitial fibrosis [38]. Persistent inflammation is very relevant in this process. The population of resident and recruited monocytes, and in

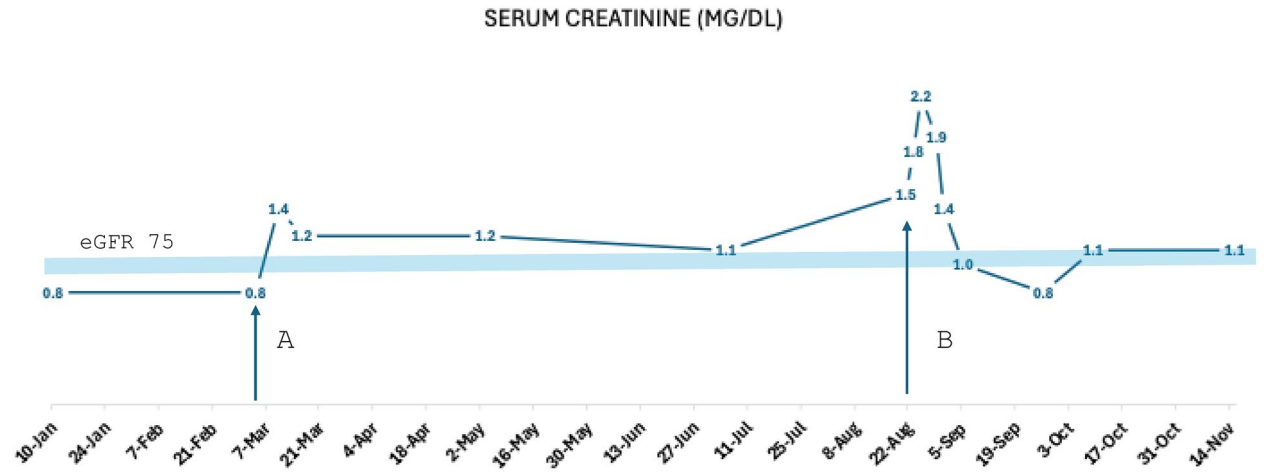

Fig. 2 Example of recurrent AKI and evaluation of renal function. Shown are serum creatinine values obtained over a 1-year period for a 63-year-old white male experiencing two episodes of acute kidney injury (AKI), **A** and **B**. Arrows indicate the dates of each admission. The horizontal line indicates the corresponding serum creatinine value representing an estimated glomerular filtration rate (eGFR) of 75 ml/min/1.73m^2 when using the original 2006 MDRD equation (1.0 mg/dl) or the 2021 race-free CKD Epi equation (1.1 mg/dl). The March 7th admission (**A**) occurred in the context of elective surgery and the 0.8 mg/dl admission value is likely at baseline given the prior value of the same. Using either 1.0 or 1.1 mg/dl, either eGFR equation would have over-estimated his baseline and might have led to the assumption that values in May and July represented recovery when in reality, renal function did not recover to baseline. AKI episode **B** was in the context of an admission to the Intensive Care Unit (ICU) for community acquired pneumonia and sepsis. At this point, his new baseline (following the prior AKI episode) would have been 1.1 mg/dl and the admission value of 1.5 mg/dl was indicative of AKI on admission. If 1.5 mg/dL had been used as a baseline, the 2.2 mg/dL peak creatinine might have been interpreted as AKI stage 1 rather than stage 2. Furthermore, the 1.4 mg/dl value two weeks later might have been misinterpreted as recovery at that point whereas subsequent values indicated a true baseline of 1.1 mg/dl. Also of note, the nadir value of 0.8 mg/dl is not a baseline value but likely reflects loss of muscle mass associated with the episode of critical illness and thus likely represents substantially worse kidney function than the pre-operative value of 0.8 mg/dl

particular the ratio between M1 and M2 macrophages, appear to be very important [39]. Distinct patterns of cell death have been observed, including cellular apoptosis, ferroptosis or necrosis. The latter may result in necroinflammation, leading to an increased inflammatory response and favoring a profibrotic phenotype [40]. Importantly, this phenotype may emerge even as glomerular function returns to baseline [41].

Prolonged cell cycle arrest and high concentrations of pro-inflammatory mediators (i.e., MCP1, CCL2) may also increase the risk of fibrosis and loss of kidney function. SASP includes profibrotic factors, including transforming growth factor beta 1 (TGF-b1) and cellular communication network factor 2 (CCN2) [42]. TGF-b1 is produced and released by a variety of cell types, including tubular epithelial cells, glomerular cells and infiltrating immune cells (such as lymphocytes and macrophages). TGF-b1 activates fibroblasts and increases collagen production. CCN2 is recognized as a fibrotic marker in kidney tissue as it promotes epithelial-mesenchymal transition in tubular cells. Complement activation also plays a role in renal tissue repair/non-repair. In experimental models, tissue specific deletion of cell surface complement regulatory protein increases the susceptibility to renal reperfusion injury [43]. Tubular cells undergoing necrosis release extracellular high mobility group box (HMGB)-1, which triggers sterile inflammation upon AKI in mice. Intracellular HMGB-1 is a potential target to enhance kidney regeneration and to improve long-term prognosis in AKI [44]. Further, repeated episodes of renal injury, as commonly observed in critically ill patients, impair processes of tissue regeneration and decrease the likelihood of sustained recovery [6, 45].

Aging can significantly alter the regenerative capacity of the kidney. Distinct processes that explain why older kidneys are more prone to maladaptive repair after AKI include diminished proliferative reserve, an increased tendency for apoptosis, decreased functional adaptability of macrophages and an increase in the expression of TGF-b1 [46].

The nephrons that remain following kidney injury and reduction in nephron mass undergo adaption in the microcirculation and structural hypertrophy, resulting in increased glomerular filtration rate (GFR) ("single nephron hyperfiltration") [47]. Renal functional reserve (RFR) describes the capacity of the nephron mass to increase GFR from baseline in response to stimuli (e.g., protein load) [48, 49]. Persistent hyperfiltration can

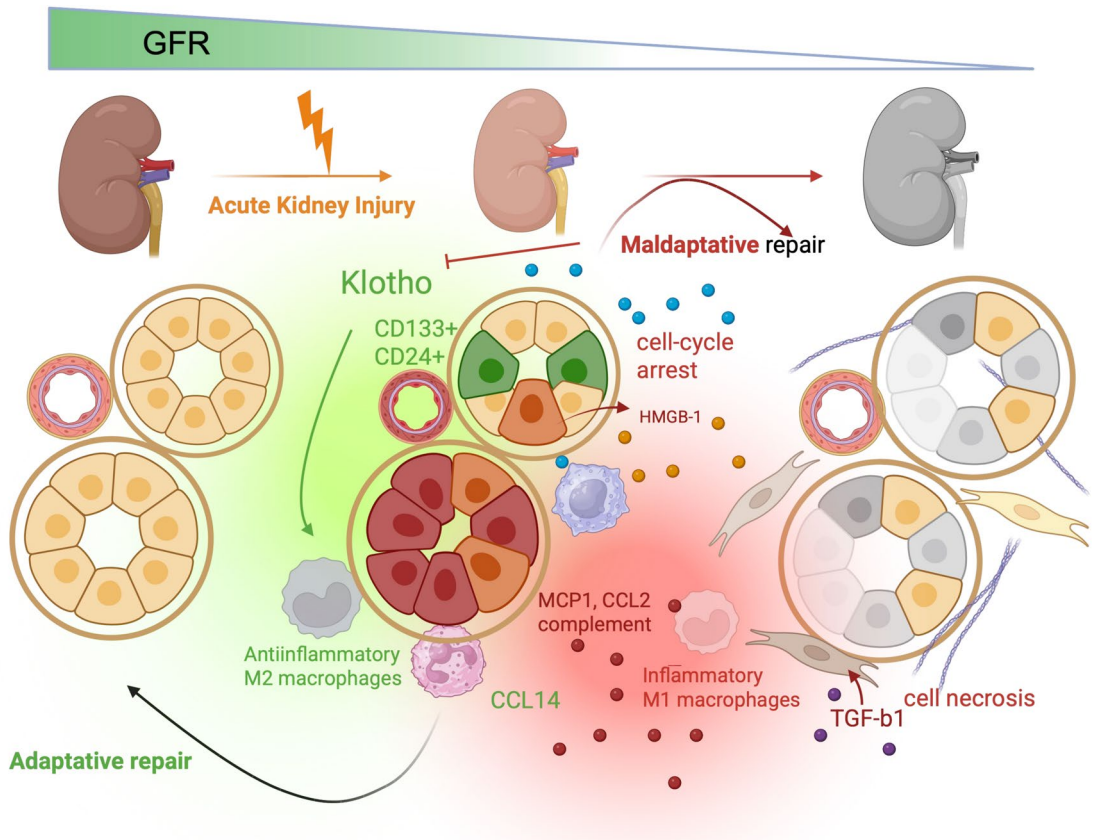

Fig. 3 Transition from AKI to renal recovery or non-recovery. AKI is an inflammatory process resulting in tubular cell damage, release of inflammatory mediators [including monocyte chemoattractant protein 1 (MCP1), chemokine C–C-motif chemokine ligand (CCL) 2 and CCL14] and initiation of cell cycle arrest. The tubular cells undergoing necrosis release extracellular high mobility group box (HMGB)-1, which triggers inflammation further. CCL14 promotes intrusion of monocytes into the renal interstitial compartment and their transformation to macrophages. Klotho, a transmembrane protein, helps to regulate fibroblast growth factor signaling and stimulates macrophage polarization towards the anti-inflammatory M2 phenotype. Adaptive repair following AKI depends on the capacity of immature tubular cells to replace irreversibly damaged epithelial cells and regenerate nephron segments. Some parietal cells (CD133 +, CD24 +) are renal progenitor cells that have the capacity to differentiate into renal epithelial cell types, enabling recovery of tubular and glomerular structures. While brief periods of G1 cell cycle arrest are protective, prolonged cell cycle arrest, especially at G2, leads to maladaptive repair and development of tubulointerstitial fibrosis. The population of resident and recruited monocytes, and in particular the ratio between pro-inflammatory M1 and anti-inflammatory M2 macrophages play a role. Tumor growth factor β (TGF-β) is a cytokine released by damaged tubular epithelial cells and glomerular cells and infiltrating lymphocytes and macrophages. One of the roles of TGF-β is to activate fibroblasts and stimulate collagen production. Adaptive and maladaptive repair processes may occur simultaneously within the kidney. As a result, fully regenerated tubules may arise just as other nephrons undergo fibrosis. Glomerular filtration rate (GFR) may persist at pre-injury level due to hyperfiltration in functioning nephrons but only to decline as fibrosis progresses and glomerular sclerosis occurs

eventually lead to albuminuria, proteinuria, glomerulosclerosis and reduced RFR, and is associated with an increased susceptibility to recurrent AKI.

Assessment of renal function after AKI

Serum creatinine remains the most widely used measure of kidney function, both in the acute and chronic setting, but has important limitations, particularly after critical illness [50]. Sarcopenia and advanced liver disease affect creatinine generation and therefore lead to overestimation of the extent of renal recovery [51]. Further, as a freely filtered molecule, in steady state, serum creatinine is reciprocally related to GFR. However, with decline of glomerular function, tubular secretion of creatinine increases, and as a result, measured creatinine clearance may over-estimate true GFR by 10–20% [52].

Although the influence of muscle mass is partially considered in current equations to estimate GFR by correcting serum creatinine for an individual's age, sex and race, the application of creatinine-based formulae to estimate GFR implicitly assumes equal muscle mass in individuals of the same, age and race. Thus, they systemically and substantially over-estimate kidney function in patients with muscle loss after critical illness [27, 53, 54].

Cystatin C and proenkephalin A are alternative biomarkers of glomerular function [55, 56]. Cystatin C is freely filtered and almost entirely reabsorbed in the proximal tubules. Although it is not affected by muscle mass or tubular secretion, serum concentrations are altered by inflammatory and metabolic state and can be confounded by certain drugs, including corticosteroids [56, 57]. Proenkephalin offers a real-time estimation of glomerular filtration and improves the early identification of renal recovery or persistent dysfunction following AKI [55].

Similar to serum creatinine, an equation to estimate steady state GFR from cystatin C has been developed as well as an equation using both creatinine and cystatin C. However, these equations have not been well investigated in patients recovering from AKI [58]. Given the potential confounding to both creatinine and cystatin C, formal measurement of GFR using a gold standard technique (i.e., excretion of an exogenous indicator such as iohexol) may be required in situations where accurate information about kidney health after AKI is needed [59]. Obviously, without a measured GFR at baseline, it would not provide information about the degree of recovery/non-recovery but might capture CKD diagnosis missed by serum creatinine in patients with low muscle mass.

Importantly, even if GFR has returned to baseline, this may not assure kidney health [60]. Healthy kidneys maintain a RFR, i.e., the capacity to increase their filtration function in response to physiological stress [61]. Determining RFR may be important when evaluating 'true' recovery since restoration of baseline serum creatinine and GFR at the expense of hyperfiltration of remaining nephrons is a risk factor for future kidney disease [62]. At present, assessment of RFR requires serial measurement of GFR before and after a protein load and is not widely implemented in clinical practice.

Albuminuria and proteinuria are common after AKI. Albumin is the principal component of urinary protein in most kidney diseases. Albuminuria/proteinuria indicates renal damage but is also nephrotoxic and represents a strong prognostic marker for CKD progression and associated cardiovascular risk [63]. Proteinuria may reflect glomerular hyperfiltration and injury (a possible surrogate of loss of RFR) or chronic tubular injury and interstitial fibrosis or both. Given its ease of measurement, determining albuminuria or proteinuria is recommended after an episode of AKI as part of the evaluation for ongoing kidney damage and risk stratification in all AKI survivors [64, 65]. Epidemiologic data demonstrate a strong relationship between the quantity of urine albumin with both kidney and cardiovascular risk even at low levels, and assays to measure albumin are more precise and sensitive than assays to measure urine protein [66, 67].

Other biomarkers of kidney damage may also have a role in characterizing renal recovery by reflecting severity of kidney injury and/or indicating local inflammatory processes that might lead to fibrosis [56, 68]. (Supplementary S1) However, to date, most of these biomarkers have been evaluated to detect the development or persistence of AKI but not the degree of recovery. Importantly, there is likely to be significant overlap in processes causing acute and chronic renal interstitial injury.

When assessing renal function after AKI, it is important to remember the physiological decline of kidney function with aging [69]. Up to a certain point, this physiological loss of functioning nephrons is compensated by hyperfiltration and hypertrophy of the remaining nephrons [70]. The net effect is near-constancy of serum creatinine while real GFR declines. However, RFR is reduced and susceptibility to AKI is increased. Not surprisingly, age, chronic hypertension and diabetes mellitus are risk factors for CKD and ESKD after AKI [71].

Prediction of non-recovery of renal function

After AKI, several trajectories of kidney function have been observed depending on the underlying cause, varying in speed and extent of recovery as well as the risk of relapse and recurrence [3]. Patients with functional AKI often recover renal function quickly following hemodynamic and fluid resuscitation. Sepsis-associated AKI, ischemic/surgical AKI, and nephrotoxic AKI, each require different treatments and present with distinct patterns of kidney function recovery, including differences in the speed of recovery, the risk of persistent AKI, the likelihood of relapse, and the potential for progression to CKD. Tools are available to identify patients with high risk of non-recovery. For instance, the RUBY study identified CCL14 as best predictor of persistent severe AKI, providing opportunities for early identification and potential intervention [72]. Importantly, receipt of renal replacement therapy (RRT) is strongly associated with adverse kidney outcomes, not just as a measure of severity of AKI/AKD, but also as exposure to RRT may impact the kidneys' ability to recover [73].

Novel biomarkers have emerged as valuable additional tools to predict AKI outcomes. (Supplementary Table 1) One such biomarker, CCL14, has demonstrated strong predictive ability for development of persistent severe AKI (defined as AKI stage 3 lasting for $\geq$72 h, death or RRT) in patients with moderate to severe AKI [72]. The accuracy of this prediction can be enhanced by combining it with a clinical test, such as the furosemide stress test, which provides additional insight into tubular cell function [74]. This combined approach offers a method

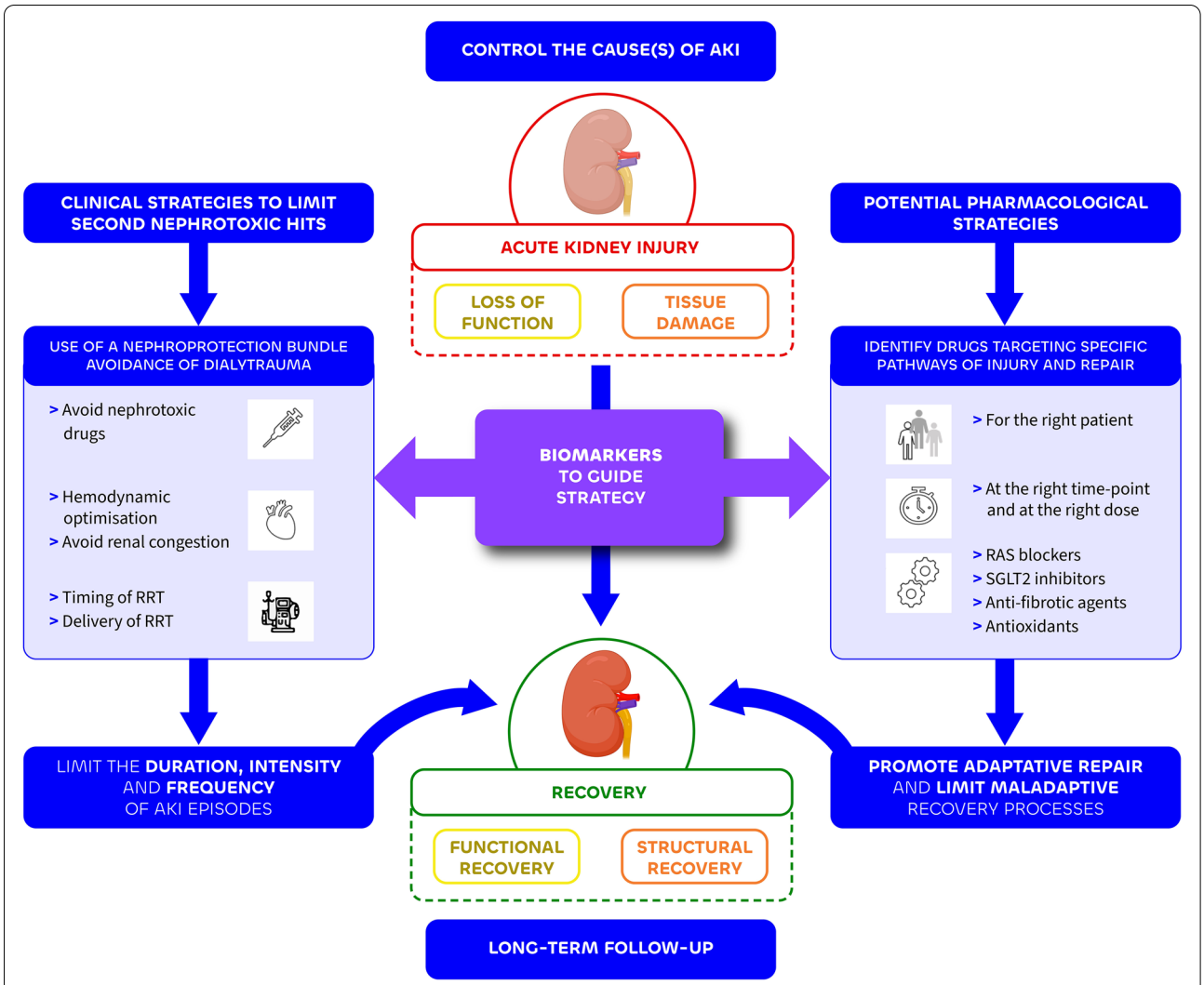
CONTROL THE CAUSE(S) OF AKI
ACUTE KIDNEY INJURY
LOSS OF FUNCTION
TISSUE DAMAGE
CLINICAL STRATEGIES TO LIMIT SECOND NEPHROTOXIC HITS
USE OF A NEPHROPROTECTION BUNDLE AVOIDANCE OF DIALYTRAUMA
> Avoid nephrotoxic drugs
> Hemodynamic optimisation
> Avoid renal congestion
> Timing of RRT
> Delivery of RRT
POTENTIAL PHARMACOLOGICAL STRATEGIES
IDENTIFY DRUGS TARGETING SPECIFIC PATHWAYS OF INJURY AND REPAIR
> For the right patient
> At the right time-point and at the right dose
> RAS blockers
> SGLT2 inhibitors
> Anti-fibrotic agents
> Antioxidants
BIOMARKERS TO GUIDE STRATEGY
LIMIT THE DURATION, INTENSITY AND FREQUENCY OF AKI EPISODES
PROMOTE ADAPTATIVE REPAIR AND LIMIT MALADAPTIVE RECOVERY PROCESSES
RECOVERY
FUNCTIONAL RECOVERY
STRUCTURAL RECOVERY
LONG-TERM FOLLOW-UP

Fig. 4 Risk factors and potential opportunities after AKI. Abbreviations: *RRT* renal replacement therapy, *RAS* renin angiotensin system, *SGLT2* sodium-glucose cotransporter-2

for identifying AKI patients at risk of requiring RRT but also allows identification of patients with preserved tubular function and low risk of progression. Other biomarkers of risk and progression of CKD, such as Dickkopf related protein 3 (DKK-3) [75] and Soluble Urokinase Plasminogen Activator Receptor (suPAR) [76] have also been shown to predict risk of AKI development and progression.

Strategies to promote renal recovery

At present, the armamentarium available for facilitating the transition from AKI to recovery is limited [77]. Strategies to promote renal recovery consist of timely management of the underlying illness that is contributing to AKI, measures that preserve renal function, including optimization of hemodynamics and fluid status, and avoidance of exposures that may cause more renal injury or prevent natural repair processes (Fig. 4). Drug stewardship is particularly important [78]. In patients receiving RRT, mitigation of dialytrauma is crucial (Table 2). Excessive fluid administration has also been associated with development and progression of AKI and delayed recovery [79–82]. The potential mechanisms include venous congestion and intra-renal compartment syndrome as a result of the kidneys being encapsulated organs. Resolution of renal congestion has been shown to improve renal function [83].

Table 2 Role of dialytrauma in renal recovery

Aspects of RRT	Current evidence	Knowledge gap
Timing of initiation	Accelerated initiation of RRT is associated with higher dialysis dependence at day 90	Need for studies exploring different timing of RRT initiation in special populations e.g., children, pregnant women, patients with cirrhosis, or patients who require ECMO/ECCO2R
Modality	Conflicting evidence of RRT modality on renal recovery	Role of RRT modality in renal recovery
Intensity	More intensive RRT is associated with higher dialysis dependence on day 28 compared to standard intensity	Impact of lower effluent dose (< 20 ml/kg/hr) of CRRT on renal recovery
Membrane	No difference in kidney recovery rates between RRT with low-flux versus high-flux membranes	Role of hemoadsorption and extracorporeal blood purification techniques on renal recovery
Anticoagulation	No difference in kidney recovery rates between RRT with RCA versus heparin	Role of coagulation system in renal recovery
Weaning	Prolonged RRT duration is associated with reduced chances of renal recovery	Lack of reliable indicators of renal recovery during RRT
Fluid removal rate	Excessive fluid removal is associated with hemodynamic instability; limited fluid removal is associated with prolonged fluid overload	Optimal rate of fluid removal during course of AKI is unknown
Hemodynamic optimization	Intradialytic hypotension is associated with reduced chances of renal recovery; administration of angiotensin II in patients with shock receiving RRT was associated with earlier liberation from RRT	Optimal MAP and best vasopressor to facilitate renal recovery are unknown
Sodium profiling	Strategy used in chronic dialysis to facilitate hemodynamics but limited data in AKI	Role of sodium profiling in CRRT and SLED
Albumin administration	Can support fluid removal in patients with hypoalbuminemia; consensus guidelines do not recommend	Role of albumin administration to facilitate renal recovery during RRT
Temperature	Lower temperature increases MAP during RRT	No data whether temperature adjustment facilitates renal recovery

Abbreviations: *AKI* acute kidney injury, *CRRT* continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *ECCO2R* extracorporeal CO2 removal, *MAP* mean arterial pressure, *RCA* regional citrate anticoagulation, *RRT* renal replacement therapy, *SLED* slow extended dialysis

Prevention of dialytrauma

The impact of timing of RRT on recovery is unclear. The multinational Standard versus Accelerated Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI) trial in adults demonstrated that patients randomized to accelerated RRT initiation had a higher likelihood of requiring dialysis at day 90 compared to patients in the standard RRT initiation group (10% vs. 6%, relative risk 1.74 [95% CI, 1.24–2.43]) [84]. In contrast, data from The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) registry in children revealed a 3% increased risk of major adverse kidney events at 90 days (MAKE-90) for each one-day delay in continuous renal replacement therapy (CRRT) initiation (odds ratio 1.03 [95% CI, 1.02–1.04]) [85]. Further, the influence of RRT initiation on renal recovery in specific populations, such as pregnant women, patients with cirrhosis, or individuals on extracorporeal membrane oxygenation remains unknown.

The impact of RRT modality on renal recovery remains uncertain [73, 86–93]. A secondary analysis of the STARRT-AKI trial concluded that CRRT as the initial modality was associated with less adverse events and a lower risk of dialysis dependency at 90 days [94]. Other studies have shown no difference and more research is awaited. Two randomized controlled trials (RCTs) comparing acute peritoneal dialysis (PD) and intermittent hemodialysis (IHD) in patients with AKI showed that recovery of kidney function occurred on average 3 days earlier in patients treated with PD [95, 96]. The reasons for this were not clear but it is possible that PD was associated with better cardiovascular stability. Another theory is that PD does not expose the patient to an extracorporeal circuit and the resulting pro-inflammatory state. However, other trials showed no difference in renal recovery between patients randomized to PD versus intermittent dialysis [97]. A Cochrane review of studies published before May 2017 concluded that there were no significant differences in recovery of renal function between patients treated with PD or extracorporeal therapies [98].

Intensity of RRT was investigated in the ATN and the RENAL trials, leading to current recommendations to administer a dose of 20–25 ml/kg/h for CRRT and a weekly Kt/V of 3.9 for IHD [20, 99]. Individual patient data analysis of seven RCTs assessing different RRT

doses showed that higher intensity RRT did not affect mortality but increased the risk of dialysis dependence at day 28 [100]. Studies are ongoing investigating the role of lower doses. (NCT06014801, NCT06021288, NCT06446739).

Both, inadequate fluid removal resulting in prolonged fluid overload, and excessive fluid removal causing hemodynamic instability are detrimental to renal recovery and patient outcomes [82, 101]. Hemodynamic instability during RRT, often manifested as intradialytic hypotension, can compromise renal blood flow, reduce glomerular filtration, contribute to tubular injury and delay renal recovery [101]. In one study, the incidence of hypotension within the first hour of CRRT initiation was 43% [102]. A meta-analysis on interventions to prevent hemodynamic instability during RRT suggests that higher dialysate sodium, lower temperature, and individualized ultrafiltration rates could reduce hemodynamic instability [101]. However, most studies were small, and the overall evidence base remains limited.

A recent RCT in three French centers compared a strategy of no ultrafiltration in the first 72 h after starting RRT to targeting 100 mL/h net ultrafiltration for 72 h, coupled with protocolized assessments of preload responsiveness [103]. The study achieved an approximately 5L lower cumulative fluid balance at 72 h in the intervention group without a significant increase in hemodynamic instability but there were no differences in mortality or organ recovery. Several studies are ongoing to define optimal net ultrafiltration targets and assess the safety and efficacy of protocolized fluid removal strategies (e.g., NCT05817539, NCT06071026, NCT05473143, NCT05214729).

In a randomized, crossover trial involving 65 patients with AKI or ESKD and serum albumin < 3 g/dL who required in-hospital hemodialysis, the use of 25% albumin improved the lowest intradialytic systolic blood pressure and enabled better fluid removal compared to saline administration but rate of renal recovery was not evaluated [104]. However, a consensus guideline from the International Collaboration for Transfusion Medicine suggested not to use albumin for fluid removal or prevention of intradialytic hypotension in patients undergoing RRT based on lack of data confirming cost-effectiveness [105]. Whether interventions to limit interdialytic weight gain and/or to prevent intradialytic hypotension in patients treated with intermittent RRT modalities facilitate renal recovery has not been investigated formally.

Pharmacological interventions

In the last 10 years, a range of treatments for CKD have become available to both alter rates of decline in GFR and improve cardiovascular health. However, these strategies are not yet being systematically targeted at AKI survivors. Conversely, if patients are already on such therapies, they are often stopped during an AKI episode and may not be recommenced, typically unintentionally, after resolution of AKI.

The renin–angiotensin system (RAS) makes a significant contribution to hemodynamic regulation during AKI. Vasoconstriction of the renal vasculature from activation of the RAS can result in further kidney damage and renal fibrosis [106]. Use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) to block the RAS is linked with improved renal outcomes [107–110]. The most likely underlying pathways supporting benefit from ACEIs/ARBs are a reduction of glomerular pressure, control of blood pressure, attenuation of inflammation and oxidative stress to prevent proteinuria and renal fibrosis. While ACEIs and ARBs offer the potential to prevent fibrosis and delay the development of CKD, they have not been shown to reverse fibrosis.

Like ACEIs and ARBs, sodium-glucose cotransporter-2 (SGLT2) inhibitors reduce intraglomerular pressure impacting the mitigation of renal injury progression, thereby offering renoprotection. Despite potential concerns about an increased risk of AKI associated with SGLT2 inhibitor use in acute illness, these agents may provide benefits by reducing CKD progression and recurrent AKI in patients with diabetes and a recent AKI episode [111]. Further, SGLT2 inhibitors may offer potential antifibrotic effects to promote renal recovery [112, 113]. A meta-analysis of 13 RCTs comparing SGLT2 inhibitors with placebo in diabetic and non-diabetic patients concluded that allocation to an SGLT2 inhibitor reduced the risk of kidney disease progression by 37% (relative risk [RR] 0·63, 95% confidence interval [CI] 0·58–0·69) and the risk of AKI by 23% (RR 0·77, 95% CI 0·70–0·84) [114].

The American Diabetes Association recommends to avoid SGLT2 inhibitors during severe illness, prolonged fasting and before surgical procedures [115]. However, the EMPEROR (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure) trial showed that abrupt cessation of SGLT2 inhibitors may have negative consequences [116]. Six-thousand-and-ninety-nine patients with heart failure were randomly assigned to SGLT2 inhibitor or placebo for 1 to 3 years and then prospectively withdrawn (by protocol) from treatment. While the risk in the placebo group remained unchanged, in patients withdrawn from SGLT2 inhibitor, the risk of cardiovascular death and hospitalization for heart failure increased from 10.7 [95% CI 9.0–12.6] to 17.0 [95% CI 12.6–22.1] events per 100 patient-years.

There are multiple mechanisms of antifibrotic activity, including extracellular matrix modulation, interleukin-11

signaling inhibition, inhibition of connective tissue growth factor and platelet-derived growth factor signaling, and inhibiting the WNT signaling pathway by targeting naked cuticle homolog2. The drugs targeting these mechanisms are being studied to prevent AKI progression to CKD [117]. Antifibrotic agents may also have a role in assisting with recovery [117]. Pirfenidone provides antifibrotic activity by targeting the TGF-β signaling pathway and has been evaluated in preclinical studies for over 2 decades, [118] but the benefits have not been confirmed in clinical trials [119].

Antioxidants offer the prospect to interfere with oxidative stress that has been identified as a significant cause of kidney injury. Specifically, pyridoxamine antioxidant activity is linked to its ability to inhibit advanced glycation end (AGE) products. The pre-clinical studies suggested that it may have potential to reduce the severity of kidney injury, enhance renal recovery and prevent CKD after AKI [120]. Clinical trials are still needed to determine the role in AKI.

The severity and duration of AKI are key factors in predicting renal outcomes and should be considered when selecting patients for pharmacologic intervention studies aimed at renal recovery post-AKI. Further, some of the investigational products have dose and phase dependent effects and need to be administered at optimal doses at the right time when evaluating their role.

Long-term impact of renal recovery

The risk of CKD and kidney failure increases with greater KDIGO AKI stage in a graded fashion [5, 121]. Animal studies suggest a common pathway between maladaptive repair after AKI and CKD progression, supporting the importance of the recovery process for long-term renal outcomes [122]. One of the largest studies to date examining long-term impact of AKI in a population-based cohort assessed recovery at 90 days, or closest available, after the AKI event [18]. All-cause mortality and a combined renal outcome of sustained doubling of serum creatinine or progression to ESKD were evaluated. Recovery was assessed in 3231 patients over a median period of 34 months with 69.5% recovering to 25% of their baseline and a total of 2.1% progressing to ESKD. However, 30.8% died with a higher observed mortality when renal recovery failed to achieve 55% of baseline. A similar population-based study in over 160,000 patients demonstrated that the adjusted hazard ratio (aHR) of CKD increased with AKI duration (aHR = 1.13 [95% CI, 1.08–1.19] for persistent AKI and 1.36 [95% CI, 1.30–1.41] for AKD compared with rapid reversal AKI) [10]. AKI duration was also associated with increasing rates of heart failure, ischemic heart disease, and peripheral artery disease. When considering patients receiving RRT for AKI, the outcomes are, unsurprisingly, even worse. Using the US Renal Data System, a cohort of 1,045,540 patients were examined with 3% of patients on incident dialysis identified as having kidney failure attributed to AKI of whom 35% eventually recovered kidney function, defined as no longer needing RRT, with most recovering within 12 months (95%) [123]. Patients with kidney failure due to AKI had both a higher 3-month mortality (15%) and 12-month mortality (35%) than those with kidney failure due to diabetes or other causes. In adjusted analyses, kidney failure due to AKI was associated with higher risk of mortality in the first 6 months followed by decreasing mortality later.

These findings are consistent across studies. Indeed, a meta-analysis of 82 studies including over 2 million patients confirmed that individuals with AKI were at increased risk of new or progressive CKD, ESKD and death [5]. There was a relationship between the severity of AKI and outcomes. Other studies have also shown an association between recovery phenotypes, in particular timing and relapses, and long-term mortality, with age-adjusted 1-year survival ranging from > 90% in patients with early reversal to less than 40% in patients never reversing [3]. Although different phenotypes of recovery may have different effects on long-term outcomes, it remains unknown whether the duration, extent or underlying pathological processes of recovery are the main determinants of prognosis.

The experimental models have shown that prolonged duration of AKI, e.g., delayed recovery, was also associated with remote organ dysfunction, mostly mediated by inflammation and neurohormonal changes [124–126]. Such crosstalk between the kidneys and distant organs can affect virtually all organ systems. The risk of major adverse cardiac events, heart failure, coronary events, and hypertension is increased in AKI survivors [127, 128]. Dialysis requiring AKI has also been associated with a higher risk of strokes and development of dementia [128, 129]. Further, associations between AKI and an increased long-term risk of severe sepsis, upper gastrointestinal hemorrhage, fractures, and malignancy have been reported [130–133].

Follow-up after AKI

With improved outcomes from hospitalized AKI, providing optimal post-AKI care is of ever-greater relevance [64]. Longer term adverse kidney outcomes include de novo CKD, CKD progression, kidney failure, further episodes of AKI, [134, 135] and key non-kidney care outcomes, including hypertension and cardiovascular disease. The goals of longer-term follow-up include prevention of further episodes of AKI, recognition and management of CKD progression, medication management,

Table 3 Select studies investigating strategies to facilitate renal recovery

Study	Objective	Population	Main outcomes/endpoints
CLEAR-AKI NCT05996835	RCT to investigate the role of TIN-816 (an ATP modulator) in sepsis-associated AKI	critically ill adult patients with sepsis-associated AKI	Primary outcome: endogenous creatinine clearance from day 1 to day 8; secondary outcomes include MAKE 90, use of RRT, survival and change of SOFA score
Development and external validation of a machine learning model for prediction of persistent AKI stage 3	Machine learning analysis to develop and validate a real-time model able to accurately predict persistent AKI in critically ill patients in the ICU	adult patients in ICU with AKI stage 2 or 3	Primary endpoint: ability to predict AKI stage 3 lasting for at least 72 h while in the ICU
COPE-AKI NCT05805709	RCT comparing a multimodal process-of-care intervention to usual care after moderate to severe AKI	adult patients with AKI stage 2 or 3 and evidence of persistent AKI	Primary outcome: hospital-free days through day 90; secondary outcomes include MAKE at 90, 180, and 365 days, recurrent AKI and quality of life
PAUSE-CRRT NCT06229990	RCT comparing protocol based-furosemide stress test versus standard care to evaluate renal recovery during CRRT	adult patients in ICU treated with CRRT for AKI	Primary outcome: free of RRT for at least 5 days; secondary outcomes include mortality, length of stay, CRRT related complications and costs
Pirfenidone effect on the Recovery of Renal Function in Septic AKI NCT02530359	RCT comparing Pirfenidone (2 different doses) versus placebo in patients with septic AKI	patients with septic AKI	Primary outcome: renal function recovery within 7 and 28 days; secondary outcomes included urine volumes, need for RRT, mortality, inflammatory markers
ALTER-AKI NCT04705896	RCT comparing albumin (20–25%) boluses versus saline boluses at the start and halfway through RRT sessions in ICU to a maximum of 14 days	ICU patients treated with RRT for AKI	Primary outcome: Organ-support-free days; secondary outcomes include RRT free days, mortality, MAKE 90, mechanical ventilation free days
SAFE-APD NCT03598387	RCT comparing automated PD versus IHD in AKI	Adult patients with AKI meeting criteria for RRT	Primary outcome: rate of renal function recovery (independence of dialysis); secondary outcomes include mortality, access related complications, length of stay in hospital, quality of life
DAKI-CKD NCT05713851	RCT comparing Dapagliflozin to placebo to avoid AKI to CKD transition	Adult patients with AKI stage 3 for less than 24 h	Primary outcome: mean change in urinary Serpin A3 levels 18 months after randomization; secondary outcomes include GFR and biomarker levels at 18 months

Abbreviations: *AKI* acute kidney injury, *ATP* adenosine triphosphate, *CKD* chronic kidney disease, *CRRT* continuous renal replacement therapy, *GFR* glomerular filtration rate, *ICU* intensive care unit, *LOS* length of stay, *MAKE* major adverse kidney event, *RCT* randomized controlled trial, *RRT* renal replacement therapy, *SOFA* Sequential Organ Failure Assessment

mitigating cardiovascular risk, transfer of information to relevant healthcare providers and patient education. The latter cannot be understated given that over 80% of hospitalized patients who experienced AKI were unaware that AKI had occurred, including patients who received RRT [136]. Follow-up of AKI survivors thus includes both in-hospital and out-patient care and ideally, an interdisciplinary personalized approach to maintain continuity of care after discharge. However, effective models of care to improve long-term outcomes remain unclear. A key challenge is the detection of unrecovered renal failure when using serum creatinine in the context of critical illness induced sarcopenia and the inability to detect structural renal injury where function is still preserved.

Currently, targeted AKI follow-up is sparsely applied, particularly in patients who experienced multi-organ failure. Even among patients who received nephrology-delivered RRT in the ICU, only 40% had nephrology follow-up within 90 days of hospital discharge [137]. The discharge summaries of patients with AKI often lack essential information about AKI, changes in medication and follow-up plans [138]. In other reports, only around 50% of such patients had their kidney function measured at all in the 6 months after discharge [139].

The studies have reported better processes of care and outcomes associated with nephrology specialist follow-up and structured post-AKI clinics, but follow-up with specialists remains challenging to coordinate [140–142]. It is acknowledged that in many settings, limited resources and logistic difficulties may preclude routine nephrology follow-up as a universal approach. While observational evidence exists that all-cause mortality is lower in those patients with early nephrology follow-up compared with a propensity matched cohort without [137], high quality evidence for such an intervention is scarce. The FUSION study examined the feasibility of randomizing survivors of AKI to early follow-up with a nephrologist or usual care [143]. Unfortunately, the trial was stopped for slow recruitment, with high rates of patients declining participation because of hospitalization-related fatigue, reluctance to add more doctors to an already complex health care team and long travel times [143]. Patients have also described prioritization of other health conditions over their kidney disease, limited awareness of AKI as a potential long-term health issue, and anxiety from competing health demands as challenges [144]. Further, healthcare providers often perceive AKI as a complex condition to manage, at times requiring clinical decisions that conflict with the treatment of other comorbidities [145].

An alternative approach is the development of follow-up pathways that enable effective monitoring and management of kidney health in the community, while appropriately targeting specialist expertise to those who require it most. In the UK, toolkits exist to facilitate tailored and timely post-AKI discharge care, including medicines reconciliation and albuminuria estimation at 3 months [146]. Triage of patients for hospital versus community-based follow-up might be aided by risk-prediction modeling [147]. However, there are currently no standards to direct the identification and management of key modifiable risk factors and more research is needed [148]. (Table 3).

Conclusions

Recovery from AKI is an active process that can easily be derailed by additional or prolonged injury. When damage to the kidney is mild such that damaged cells can be replaced, full regeneration is possible. However, new nephrons are not produced, so with extensive damage, fibrosis is the only repair that can be achieved. Current strategies to achieve recovery therefore focus on rapid identification of the mechanism of injury and minimizing ongoing or secondary insults. Unfortunately, treatment can itself exacerbate injury. Excessive use of fluids and various forms of dialytrauma impair recovery. The likelihood that repair will be maladaptive increases with age and extent/duration of injury. Notably, return of GFR to pre-injury levels does not exclude nephron loss because of RFR. Loss of this reserve predisposes to subsequent injury and hyperfiltration can lead to CKD. Whether hyperfiltration can be targeted with RAS blockers or SGLT2 inhibitors is currently unclear but the subject of ongoing research. Given that prognosis for AKI is critically tied to recovery, there is great urgency to identify effective therapies.

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Declarations

Conflicts of interest

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Ethical approval

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